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US Epidemiology of Cannabis Use and Associated Problems

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This review provides an overview of the changing US epidemiology of cannabis use and associated problems. Adults and adolescents increasingly view cannabis as harmless, and some can use cannabis without harm. However, potential problems include harms from prenatal exposure and unintentional childhood exposure; decline in educational or occupational functioning after early adolescent use, and in adulthood, impaired driving and vehicle crashes; cannabis use disorders (CUD), cannabis withdrawal, and psychiatric comorbidity. Evidence suggests national increases in cannabis potency, prenatal and unintentional childhood exposure; and in adults, increased use, CUD, cannabis-related emergency room visits, and fatal vehicle crashes. Twenty-nine states have medical marijuana laws (MMLs) and of these, 8 have recreational marijuana laws (RMLs). Many studies indicate that MMLs or their specific provisions did not increase adolescent cannabis use. However, the more limited literature suggests that MMLs have led to increased cannabis potency, unintentional childhood exposures, adult cannabis use, and adult CUD. Ecological-level studies suggest that MMLs have led to substitution of cannabis for opioids, and also possibly for psychiatric medications. Much remains to be determined about cannabis trends and the role of MMLs and RMLs in these trends. The public, health professionals, and policy makers would benefit from education about the risks of cannabis use, the increases in such risks, and the role of marijuana laws in these increases.
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Cannabis has been used in the United States since the 1800s, with public attitudes toward its acceptability and potential harmfulness varying over time (Musto, 1991). Since 1996, US state laws about the legal use of cannabis for medical and recreational purposes have changed, as have public attitudes about the safety and acceptability of cannabis use. This review aims to provide a broad overview of the epidemiology of cannabis use and associated problems in the United States. The review begins with a section on epidemiologic and public health findings about adverse behavioral, psychosocial, and psychiatric problems associated with cannabis use. These are presented in life-course order of cannabis exposure: prenatal period, childhood, adolescence, and adulthood. The section includes consideration of whether the associations are causal or not (Hall *et al*, 2016), eg, ruling out reverse causation by clarifying time order (ensuring that the problem does not precede cannabis use) and confounding (controlling for factors that increase the likelihood of both using cannabis and developing the problem). The second section covers changes in the public perception of potential harms/adverse consequences. In the third section, time trends in cannabis use and behavioral, psychosocial, and psychiatric problems are reviewed. The fourth section covers available evidence about the influence of state medical and recreational marijuana laws on the prevalence of cannabis use and associated problems, as well as on substitution of cannabis for opioids, alcohol, and psychiatric medications. Finally, implications for clinicians, policy makers, and the public are considered, and future research directions suggested.

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ADVERSE HEALTH AND PSYCHOSOCIAL PROBLEMS ASSOCIATED WITH CANNABIS USE

Prenatal Exposure

Many concerns exist about maternal use of cannabis during pregnancy and potential harm to the fetus (Volkow *et al*, 2017). Consistent with this, the American College of Obstetricians and Gynecologists recommends advising pregnant women and women contemplating pregnancy about potential risks of prenatal marijuana use in order to discourage use (American College of Obstetricians and Gynecologists Committee on Obstetric Practice, 2015). In 2007–2012 data from the National Surveys on Drug Use and

Health (Ko *et al*, 2015), 3.9% of pregnant women used cannabis in the past month, 7.0% used it in the past 2–12 months, and among past-year users, 16.2% used near daily (Ko *et al*, 2015). A recent meta-analysis indicates that infants born to women who used marijuana prenatally were more likely than others to be anemic, have low birth weight, and require neonatal intensive care (Gunn *et al*, 2016). Prenatal marijuana exposure is also linked to subsequent impaired executive functioning in school (Wu *et al*, 2011), consistent with prospective research showing associations between prenatal cannabis exposure, restricted fetal growth, and greater childhood frontal cortical thickness (El Marroun *et al*, 2016). However, understanding whether prenatal cannabis exposure is causally related to poor childhood outcomes is complicated by the fact that most pregnant cannabis users in existing studies also used other substances, limiting knowledge about effects specific to cannabis (National Academies of Sciences, 2017; Volkow *et al*, 2017). Media reports suggest that, increasingly, some women see cannabis as a natural, safe substance to use throughout pregnancy, even if they do not use other substances (The New York Times, 2017). Such trends are concerning given that risks may well exist, although the need for further research on cannabis use and pregnancy outcomes is clear.

Childhood Exposure

The onset of recreational cannabis use almost always begins in adolescence, with 'early-onset' generally referring to early adolescence, not childhood. Consistent with this, the national Monitoring The Future (MTF) study found that in 2016, the prevalence of cannabis use among eighth graders (generally age 13–14 years) was only 5.4% (The Monitoring the Future study and the University of Michigan, 2016). Therefore, the main type of cannabis exposure in childhood is unintentional, often resulting from ingestion of cannabis or a cannabis product. Although the literature does not show evidence of fatal cannabis exposures (in children or adults), acute symptoms in children can include lethargy, ataxia, dizziness, and respiratory depression (National Academies of Sciences, 2017). A recent review indicated increasing risk for pediatric cannabis exposures, especially in states with legal cannabis use (National Academies of Sciences, 2017) (see below).

Adolescent Exposure

Concerns about the risks of adolescent cannabis use, especially regular or heavy use, focus on the developing adolescent brain (Batalla *et al*, 2013; Volkow *et al*, 2014; Zalesky *et al*, 2012), poor educational outcome (Fergusson *et al*, 2015), school dropout, cognitive impairment and lower IQ (Meier *et al*, 2012), lower life satisfaction and achievement (Fergusson and Boden, 2008), and addiction (Agrawal *et al*, 2004; Chen *et al*, 2009). However, studies of these problems, particularly those related to cognitive functioning, are not considered conclusive (National Academies of Sciences, 2017) because shared risk factors could be responsible for both the early cannabis use and the impairments shown later (Volkow *et al*, 2014). Furthermore, cognitive impairment could predate the earliest cannabis use. For this reason, the large-scale Adolescent Brain Cognitive Development (ABCD) Study (National Institutes of Health, 2015) has been launched. The ABCD study aims to conduct extensive neurocognitive and brain imaging studies on children before the earliest age at onset of cannabis use, and then to repeatedly assess children who do and do not use cannabis over 10 years to determine their neurocognitive and other outcomes.

Adult Exposure

Overall mortality and fatal overdose. A number of studies have been conducted on the relationship between cannabis use and overall mortality. Unadjusted analyses show an association between cannabis use at a given point in time and overall mortality years later (National Academies of Sciences, 2017). However, after adjustment, associations are generally reduced or eliminated. Many problems exist with these data and study designs, making determination of a causal relationship difficult (National Academies of Sciences, 2017). A further complication to this research is that the cause of death noted in the mortality statistics does not always reflect acute cannabis use, as suggested by toxicology results indicating cannabis use in a series of hanging deaths (San Nicolas and Lemos, 2015) in San Francisco. There are no known cases of fatal overdose from cannabis use in the epidemiologic literature (Calabria *et al*, 2010; Hall *et al*, 2016).

An important type of harm related to cannabis use is the increased risk for injury or fatality due to intoxication while driving (Hall *et al*, 2016). The primary psychoactive component of cannabis, Δ-9-tetrahydrocannabinol (THC), impairs the motor and cognitive functions needed for safe driving (Ramaekers *et al*, 2004; Rogeberg and Elvik, 2016), making clear the causal role of cannabis in this public health problem. Cannabis use while driving has been shown to substantially increase the risk for motor vehicle crashes (Asbridge *et al*, 2012; Brady and Li, 2014; Li *et al*, 2012; National Academies of Sciences, 2017; Rogeberg and Elvik, 2016), and is implicated in fatal and nonfatal crashes (Asbridge *et al*, 2012; Brady and Li, 2014; Hartman and Huestis, 2013; Li *et al*, 2012; Ramaekers *et al*, 2004; Zhu and Wu, 2016). Injury and fatality risk for crashes may be further increased because of a link between cannabis use and failure to use seatbelts (Liu *et al*, 2016). In Canada, where medical marijuana has been legal since 2001, cannabis-attributable driving harms and costs are substantial (Wettlaufer *et al*, 2017). In addition to motor vehicle crashes, cannabis has also been implicated in fatal injuries among US pilots (McKay and Groff, 2016).

Legislation that prohibits driving while under the influence of alcohol is enforceable because roadside breathalyzer tests can detect whether a driver has exceeded a legal blood

	DSM-IV Abuse[a]	DSM-IV Dependence[b]	DSM-5 SUD[c]
Hazardous use (e.g., driving under the influence)	X	–	X
Social/interpersonal problems related to use	X	–	X
Neglected major roles to use	X	–	X
Legal problems	X	–	–
Withdrawal[d]	–	–	X
Tolerance	–	X	X
Used larger amounts/longer	–	X	X
Repeated attempts to quit/control use	–	X	X
Much time spent using	–	X	X
Physical/psychological problems related to use	–	X	X
Activities given up to use	–	X	X
Craving[d]	–	–	X
	≥1 criteria	≥3 criteria	≥2 criteria

[a] One or more abuse criteria within a 12-month period
[b] Three or more dependence criteria within a 12-month period
[c] Two or more SUD criteria within a 12-month period
[d] New criterion added in DSM-5

Figure 1. DSM-IV and DSM-5 criteria for cannabis use disorder (CUD).

alcohol concentration (BAC) limit indicating impairment that is standardized nationwide. In all 50 states, this limit is a BAC level of 0.08%, whereas for commercial drivers, a lower BAC of 0.04% is used. Furthermore, ignition interlocks, or alcohol-sensing devices connected to a vehicle's ignition to prevent it from starting if a driver has or exceeds a predetermined BAC level, are a promising avenue for preventing alcohol-involved driving risks, as they reduce fatal vehicle crashes among repeat DUI offenders (McGinty *et al*, 2017b). Unfortunately, no parallel tests or devices exist for cannabis. Cannabis metabolites can be detected in blood, blood plasma, oral fluid, and urine (Lee *et al*, 2013; Marsot *et al*, 2016), although the presence of such metabolites does not necessarily indicate the likelihood of acute intoxication, as BAC does. An accurate 'breathalyzer' test for cannabis that could be used on a widespread basis has not yet been developed. This area is greatly in need of scientific advancement. Nevertheless, roadside drug testing using various methods of testing has been introduced in a number of countries (Watson and Mann, 2016), and several US states that have legalized cannabis use, eg, California, Colorado, Oregon, and Massachusetts, are experimenting with different forms of roadside testing for driving under the influence of cannabis, including biological and behavioral tests (eg, asking drivers to indicate their ability to balance).

Addiction/substance use disorder. The *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association includes definitions of substance use disorders (SUD), including cannabis use disorder (CUD). The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV; American Psychiatric Association, 1994) was published in 1994, and was in use until 2013, when *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5; American Psychiatric Association, 2013) was published. Thus, although DSM-5 is more recent, DSM-IV definitions formed the basis of a large body of research.

For substance use disorders, including cannabis use disorders, DSM-IV defined two disorders, dependence and abuse (Figure 1). DSM-IV definition of dependence was similar to dependence diagnosis in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10; World Health Organization, 1992), and showed high empirical agreement in the US and international studies (Grant, 1996; Hasin *et al*, 1997, 2006; Pull *et al*, 1997; Rounsaville *et al*, 1993; Ustun *et al*, 1997). ICD-10 had no corresponding category for DSM-IV 'abuse', but instead, a 'hazardous use' category. Abuse and hazardous use had poor empirical agreement (Grant, 1996; Hasin *et al*, 1997, 2006; Pull *et al*, 1997; Rounsaville *et al*, 1993; Ustun *et al*, 1997). Many studies in adolescents and adults examined the DSM-IV distinction between dependence and abuse. Results were very consistent: abuse and dependence criteria formed a single, unidimensional construct (Hasin *et al*, 2013).

In DSM-5, most criteria for abuse and dependence were combined into a single disorder (Figure 1). Additional DSM-5 changes included removing the DSM-IV legal problems criterion, and adding criteria for craving and cannabis withdrawal (Hasin *et al*, 2013). In contrast to DSM-5, ICD-11 will retain dependence as the ‘master diagnosis’ (Saunders, 2017). The differences between DSM-5 and ICD-11 will doubtless generate discussion and additional studies (Saunders, 2017).

A common assumption about the risk for CUD among users is that it is rare, based on findings from 25 years ago that few cannabis users developed CUD (Anthony *et al*, 1994; Joy *et al*, 2017). However, in more recent US national data, 3 out of 10 cannabis users developed DSM-IV CUD (Hasin *et al*, 2015a). Moreover, extending analyses of DSM-5 diagnoses of CUD (Hasin *et al*, 2016), 19.5% of lifetime users met criteria for DSM-5 CUD, of whom 23% were symptomatically severe (⩾6 criteria). Of these, 48% were not functioning in *any* major role (eg, work). Thus, CUD in users is not rare and can be serious.

In terms of causality, cannabis use is clearly a necessary condition for CUD, but as not all cannabis users develop CUD, use is not clearly sufficient. The etiology of CUD is complex (Agrawal and Lynskey, 2006; Bogdan *et al*, 2016; Haberstick *et al*, 2011; Verweij *et al*, 2013b), involving both genetic (Sherva *et al*, 2016) and environmental factors. Social-ecological models of substance use (Babor, 2010; Connell *et al*, 2010; Corbett, 2001; Gruenewald, 2011; Gruenewald *et al*, 2014) assume that in general, use is increased by factors that increase availability and also desirability, by normalizing use and reducing perception of harm. If these environmental factors also increase the prevalence of heavy or frequent users, then they are likely to increase the risk for CUD.

Cannabis withdrawal. When DSM-IV was published, little was known about cannabis withdrawal. Since then, preclinical (Copersino *et al*, 2006; Goldstein and Volkow, 2011; Haney *et al*, 2004; Martinez *et al*, 2007), clinical (Agrawal *et al*, 2008; Budney and Hughes, 2006; Budney *et al*, 2004; Chung *et al*, 2008; Copersino *et al*, 2006; Goldstein and Volkow, 2011; Hasin *et al*, 2008; Martinez *et al*, 2007), and epidemiologic (Agrawal *et al*, 2008; Hasin *et al*, 2008) studies have demonstrated a cannabis withdrawal syndrome after cessation of use. This syndrome is most intense during the first week of abstinence, but can persist as long as a month after use (Budney *et al*, 2003; Copersino *et al*, 2006; Elkashef *et al*, 2008; Hall *et al*, 2016; Kouri and Pope, 2000; Milin *et al*, 2008) and has pharmacological specificity (Budney *et al*, 2007; Haney *et al*, 2004; Lichtman and Martin, 2002). Cannabis withdrawal is reported by up to one-third of regular users in the general population (Agrawal *et al*, 2008; Budney and Hughes, 2006; Hasin *et al*, 2008) and by 50–95% among heavy users in treatment or research studies (Chung *et al*, 2008; Copersino *et al*, 2006; Cornelius *et al*, 2008; Levin *et al*, 2010). The clinical significance of cannabis withdrawal is shown by the fact that it can be impairing (Allsop *et al*, 2012), that cannabis or other substances are used to relieve it, and by its association with trouble quitting use (Budney *et al*, 2008; Copersino *et al*, 2006; Levin *et al*, 2010) and worse treatment outcomes (Allsop *et al*, 2012; Chung *et al*, 2008; Cornelius *et al*, 2008; Greene and Kelly, 2014). In addition, in latent variable modeling (Agrawal and Lynskey, 2007), adding withdrawal to other CUD criteria improves model fit. In terms of etiology, cannabis withdrawal is moderately heritable (Verweij *et al*, 2013a), implicating both genetic and environmental factors.

TABLE 1 DSM-5 Cannabis Withdrawal Symptoms

Anxiety, restlessness
Depression, irritability
Insomnia/odd dreams
Physical symptoms, eg, tremors
Decreased appetite

Cannabis withdrawal is defined as three or more of the symptoms shown in Table 1 following cessation of prolonged use (American Psychiatric Association, 2013). Many of these symptoms overlap with symptoms of depressive or anxiety disorders. Withdrawal from other substances (eg, alcohol, opioids) is widely recognized (Stern *et al*, 2010). However, many professionals and members of the general public may not be aware of cannabis withdrawal (Katz *et al*, 2014), potentially leading to confusion about the benefits of cannabis to treat or self-medicate symptoms of anxiety or depressive disorders (see below).

Psychiatric comorbidity: mood, anxiety, and other substance use disorders. In 2001–2002 data from the US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; for more information, see Table 2), strong associations were found between DSM-IV cannabis use disorders and other substance and psychiatric disorders (Stinson *et al*, 2006), including alcohol and nicotine use disorders, mood disorders, anxiety disorders, personality disorders, and posttraumatic stress disorder (PTSD). Associations were also found between DSM-IV CUD and alcohol and nicotine dependence in data from the National Survey on Drug Use and Health (Wu *et al*, 2017) (NSDUH; Table 2), a series of national surveys of US household residents aged ⩾12 years. In a national database of hospitalized patients, ICD-9-CM CUD diagnoses were associated with schizoaffective/mood disorders and alcohol use disorders (Charilaou *et al*, 2017). In military veterans with ICD-9-CM CUD treated in the Veterans Health Administration, PTSD was the most common psychiatric comorbidity (Bujarski *et al*, 2016). In the 2012–2013 NESARC survey (NESARC-III, for more information, see Table 2), the comorbidity of CUD and psychiatric disorders was reexamined using DSM-5 definitions (Hasin *et al*, 2016). Again, strong, significant associations were found with other substance use disorders (alcohol, drug, nicotine), mood, anxiety, personality disorders, and PTSD (Hasin *et al*, 2016). Using DSM-5 CUD severity definitions of mild, moderate, and severe, associations with

TABLE 2 Surveys Providing Nationally Representative Time Trend Data on Cannabis Use and Cannabis Use Disorders (CUD)

Years of data collection	Ages	Sample sizes	Setting	Mode	Funder	Cannabis coverage
Monitoring the Future (MTF)						
Annually, 1991–present	8th, 10th, and 12th graders	~ 50 000/Year	School[a]	Self-administered questionnaires[a]	NIDA[b]	Current and past use, current perceived risk, disapproval, availability
National Survey on Drug Use and Health (NSDUH)						
Annually, 2002–present	⩾ 12 Years	~ 70 000/Year	Home	Self-administered interview	SAMHSA[c]	Current use, perceived risk, availability; current DSM-IV abuse, dependence, CUD
National Institute on Alcohol Abuse and Alcoholism (NIAAA)[d] Surveys						
1991–1992 NLAES[e]	⩾ 18 Years	42 862	Home	Interviewer-administered interview	NIAAA[d], NIDA[c] co-funding	Current, past, lifetime use; DSM-IV[f] abuse, dependence, CUD
2001–2002 NESARC[g]		43 093				Current, past, lifetime use; DSM-IV[f] abuse, dependence, CUD
2012–2013 NESARC-III[h]		36 309				Current, past, lifetime use; DSM-IV abuse, dependence, CUD; DSM-5[i] CUD

[a]Administered by survey staff, not available to teachers.[b]National Institute on Drug Abuse, National Institutes of Health.[c]Substance Abuse and Mental Health Services Administration.[d]National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health.[e]National Longitudinal Alcohol Epidemiologic Survey.[f]Diagnostic & Statistical Manual, American Psychiatric Association, 4th edition (published 1994).[g]National Epidemiologic Survey on Alcohol and Related Conditions.[h]National Epidemiologic Survey on Alcohol and Related Conditions–III.[i]Diagnostic & Statistical Manual, American Psychiatric Association, 5th edition (published 2013).

psychiatric disorders were stronger with more severe levels of CUD (Hasin *et al*, 2016).

Whether the relationship between cannabis use or CUD and mood or anxiety disorders is causal or not has been debated (Agrawal and Lynskey, 2014). The reasons for the strong, significant associations of CUD with mood and anxiety disorders could be because of shared common etiology, cannabis use or CUD leading to mood or anxiety disorders, or mood or anxiety disorders leading to cannabis use and subsequently to CUD. A prospective study using NESARC data suggested that after controlling for a multitude of potential cofactors, cannabis use predicted incidence of other substance use disorders but not mood or anxiety disorders (Blanco *et al*, 2016). A study of polygenic risk suggested that cannabis use or CUD shared genetic risk with major depression (Carey *et al*, 2016), as did a study of cannabis dependence using a genome-wide association approach (Sherva *et al*, 2016). Additional genetic studies suggest either common causes underlying the comorbidity between CUD and major depression (Hodgson *et al*, 2017) or a causal effect of CUD on major depression (Smolkina *et al*, 2017). Thus, the nature of the relationship between cannabis use or CUD and psychiatric comorbidity remains a topic of debate.

Psychiatric comorbidity: psychotic disorders. Cannabis use and psychosis are associated (Charilaou *et al*, 2017). For example, in 30 studies of healthy controls and ultra-high-risk (UHR) individuals (with subclinical psychotic symptoms and/or genetic risk and impaired functioning), a meta-analysis (Carney *et al*, 2017) showed that UHR individuals had higher rates of cannabis use and CUD, and UHR cannabis users had higher rates than nonusers of positive psychotic symptoms (unusual thought content, suspiciousness). Epidemiologic efforts to determine causation have focused on long-term prospective studies in which the time order of cannabis use and onset of psychosis indicators can be determined. For example, in 1265 children born in Christchurch, New Zealand, in 1977 assessed repeatedly, daily cannabis users later had higher rates of psychotic symptoms at age 18–25 years, controlling for many fixed and dynamic confounders (Boden *et al*, 2007). In this sample, structural equation modeling showed a significant pathway from cannabis to psychosis, but not from psychosis to cannabis use (Fergusson *et al*, 2015), supporting a causal relationship of cannabis use to development of psychotic symptoms. In a recent review (Gage *et al*, 2016), 10 prospective studies were considered, including a national record study of >50 000 male Swedish conscripts (Zammit *et al*, 2002). The review found a significant relationship between earlier cannabis use and later development of psychosis, and called for studies to determine the effect of different strains of cannabis on risk, and to identify particularly susceptible high-risk groups (Gage *et al*, 2016). A meta-analysis of 7 prospective studies of UHR samples (Kraan *et al*, 2016) did not support a relationship between cannabis use and psychosis onset. However, 5 of the studies ascertained CUD diagnoses at baseline, and in these studies, CUD was a significant predictor of subsequent psychosis. Both reviews of prospective studies (Gage *et al*, 2016; Kraan *et al*, 2016) noted concerns about elevated risk from high-THC cannabis. Although some debate remains about the causal link between cannabis and psychosis (Haney and Evins, 2016), a comprehensive review of reviews concluded that cannabis use is likely to increase psychosis risk, with increasing levels of use leading to increased risk (National

Academies of Sciences, 2017). Furthermore, cannabis use has been characterized as one of the strongest modifiable risk factors for developing a psychotic disorder, with a recommendation that a child or teen with a family history of psychosis or prodromal symptoms should be informed of the risks and counseled strongly not to use cannabis (Weiss *et al*, 2017). As the legalized recreational market in the US increasingly distributes stronger forms of cannabis, eg, vaping, dabbing, and rosin (Baumann and Scheinbaum, 2016), further studies of the relationship of cannabis to psychosis are warranted, as well as public and professional education about the risks.

Psychiatric comorbidity: nicotine use disorders. The association of cannabis and nicotine use disorders merits attention because of the most common route of administration of both substances, which is smoking, and also because cannabis and nicotine co-use can intensify cannabis effects (Penetar *et al*, 2005; Rabin and George, 2015; Wang *et al*, 2016b), although not all studies agree on this point (Haney *et al*, 2013). Individuals who use both cannabis and tobacco have greater risk of respiratory distress than cannabis-only users or tobacco-only users (Agrawal *et al*, 2012), although cannabis has not been shown to be associated with increased rates of lung cancer (Tashkin, 2015). The co-occurrence of cannabis and tobacco use could have many possible explanations including predisposing genetic factors, peer influences, availability, and social milieu (Agrawal *et al*, 2012).

TRENDS IN PUBLIC PERCEPTIONS

Inverse Relationship between Perceived Harmfulness of Cannabis and Likelihood of Use

Perceived harmfulness of cannabis has long been considered an important factor preventing adolescent cannabis use (Janz and Becker, 1984; Keyes *et al*, 2016; Piontek *et al*, 2013; Schmidt *et al*, 2016). MTF, a series of annual national school surveys of US adolescents in eighth, tenth, and twelfth grades (13–14, 15–16, and 17–18 years of age; see Table 2 for more information about the MTF surveys) provided the earliest evidence of an inverse relationship between perceived harmfulness and cannabis use (Bachman *et al*, 1988, 1998; Johnston *et al*, 1981). This relationship has now been shown repeatedly (Pacek *et al*, 2015; Swaim, 2003), including an international study in 32 countries (Piontek *et al*, 2013). An inverse relationship between perceived harmfulness and cannabis use has also been demonstrated for US adults in the annual NSDUH (see Table 2 for more information about the NSDUH surveys; (Compton *et al*, 2016).

Increasing Public Perception That Cannabis Is Harmless

Among US students in the MTF surveys of students, the perception that regular use of cannabis is risky declined substantially since 2004–2005 (The Monitoring the Future study and the University of Michigan, 2016); rates of decline ranged from 50 to 80%. In 2016, only ~30% of twelfth graders perceived such risk. The perception that cannabis use is risky also declined among adults. Among NSDUH adult participants, the perception that cannabis use involves great risk declined from 50 to 33% between 2002 and 2014, whereas the perception that use involves no risk increased from ~6 to 15% (Compton *et al*, 2016).

TRENDS IN CANNABIS POTENCY, USE, AND ASSOCIATED PROBLEMS

Time Trends in Cannabis Potency

Over the past four decades, cannabis potency, indicated by the THC content in seized samples, has approximately doubled worldwide (Cascini *et al*, 2012; Hall *et al*, 2016), including in the United States (ElSohly *et al*, 2016). In the early 1990s, the average THC content in confiscated US marijuana samples was ~3.7%, whereas in 2014 it was ~6.1% (National Institute on Drug Abuse, 2017). This increase is relevant to epidemiologic study of time trends in problems associated with cannabis use because cannabis with higher THC concentrations is more likely to increase risks associated with use (Englund *et al*, 2017). However, in states that pass recreational marijuana laws, the potency of legally purchased cannabis may be more relevant to public health (see below).

Time Trends in Prenatal Cannabis Exposure

Among NSDUH participants aged 18–44 years who were pregnant, the estimated prevalence of past-month cannabis use increased 62% between 2002 and 2014, from 2.4 to 3.9% (Brown *et al*, 2017). In 2014, the rate of past-month cannabis use was highest among pregnant women aged 18–25 years, 7.5% (Brown *et al*, 2017).

Time Trends in Childhood Exposure

Using data from the National Poison Data System to investigate accidental cannabis exposures in children <6 years old (Onders *et al*, 2016), the annual rate of exposures increased from 4.2 per million children in 2000 to 10.4 per million in 2013.

Time Trends in Adolescent Cannabis Use

Among NSDUH participants aged 12–17 years, past-month cannabis users fluctuated between 8.2% in 2002 and 7.4% in 2014 (Azofeifa *et al*, 2016a, b), with no significant overall increases or decreases. Findings from the MTF student surveys also showed that over the same period, rates of cannabis use fluctuated, with some increases up to around 2010, and either stabilization (twelfth graders) or decreases (eighth and tenth graders) from then until 2016 (The Monitoring the Future study and the University of Michigan, 2016). A study of NSDUH participants aged 12–17 years indicated that between 2002 and 2013, the prevalence of CUD decreased (Grucza *et al*, 2016b), another indicator that cannabis use/problems has not increased among adolescents in recent years.

Time Trends in Adult Cannabis Use, CUD, and Other Indicators of Cannabis-Related Problems

Between 2002 and 2014, past-month cannabis use in NSDUH participants aged 18–25 years increased from 17.3% in 2002 to 19.6% in 2014, a significant overall increase (Azofeifa *et al*, 2016b), with most of the increase occurring since 2007. Among NSDUH participants ⩾26 years, past-month use also increased significantly between 2002 and 2014 (Azofeifa *et al*, 2016b), from 4.0 to 6.6% in 2014. In this age group, the increase started in 2008 (Compton *et al*, 2016). Increases occurred across gender, region, educational level, and employment status (Azofeifa *et al*, 2016b), with higher rates in males and unemployed participants. Other indicators of adult cannabis use also showed significant increases in NSDUH participants during this period, including first-time use and daily/near-daily use (Compton *et al*, 2016). Additional studies of NSDUH data showed greater increases in cannabis use among males, especially those with lower incomes (Carliner *et al*, 2017). However, although daily or near-daily use increased in the entire sample and higher frequency of use is correlated with the risk for a substance use disorder (Compton *et al*, 2009), NSDUH data did not show increases in the prevalence of adult CUD (Compton *et al*, 2016) between 2002 and 2014.

Another source of data on adult trends were surveys conducted by the National Institute on Alcohol Abuse and Alcoholism (NIAAA): the NESARC, conducted in 2001–2002, and the NESARC-III, conducted in 2012–2013 (see Table 2 for more information about the NIAAA surveys). The past-year prevalence of cannabis use in 2001–2002 and 2012–2013 was 4.1% and 9.5%, respectively, a significant increase (Hasin *et al*, 2015a, 2017). Significant increases in use were also found across demographic subgroups (sex, age, race/ethnicity, education, marital status, income, urban/rural, and region). The past-year prevalence of DSM-IV CUD was 1.5% in 2001–2002 and 2.9% in 2012–2013, also a significant increase (Hasin *et al*, 2015a, 2017). Increases in the prevalence of CUD between 2001–2002 and 2012–2013 were also statistically significant across demographic subgroups.

The NSDUH and NESARC surveys were consistent in showing increases in adult cannabis use. However, their findings differed regarding time trends in the prevalence of CUD. Methodological differences between the surveys have been discussed as one possible explanation of the discrepant findings (Compton *et al*, 2016; Grucza *et al*, 2016a, c). Another approach to understanding the differences is to determine the consistency of the findings of these surveys with other national indicators of cannabis-related problems or CUD over the same time period (Hasin and Grant, 2016). The NESARC to NESARC-III findings on increases in the

TABLE 3 Additional Sources of Information on Time Trends in Cannabis-Related Outcomes

Authors	Data source	Time period	Sample size	Age range	Condition for which increased prevalence was shown over period
Bonn-Miller *et al* (2012)	Veterans Health Administration national database	2002, 2008, 2009	1 141 690 Patients	Mean, 53	ICD-9-CM cannabis use disorders
Johnson *et al* (2012)	California roadside surveys	2007 and 2010	1707	Median, 29	Cannabis detected in oral samples or breath tests of weekend nighttime drivers
Brady and Li (2014)	Fatality Analysis Reporting System (FARS)	1999–2010	23 591 Driver decedents	Not reported	Cannabinol in blood of drivers fatally injured in vehicle crashes
Jehle *et al* (2015)	National Burn Repository	2002–2011	73 725 Patients	⩾12 Years	Prevalence of cannabis detected in urine drug screens of patients with burn injuries
Zhu and Wu (2016)	US Drug Abuse Warning Network (DAWN)	2004–2011	2 823 321 Visits	⩾12 Years	Cannabis-only emergency room visits
Gubatan *et al* (2016)	Massachusetts General Hospital gastroenterology clinic patients	1986–2013	190 303 Patients	Mean, 47	ICD-9-CM cannabis use disorders
McKay and Groff (2016)	US Civil Aerospace toxicology database; National Transportation Safety Board aviation accidents	1990–2012	6677 Pilot decedents	Mean, 50	Cannabinol in blood or tissue of fatally injured pilots
Charilaou *et al* (2017)	U.S. National Inpatient Sample, discharge diagnoses	2002–2011	7 Million discharges per year	⩾18 Years	Proportion of hospital discharge diagnoses involving ICD-9-CM cannabis use disorders
Shi (2017)	State Inpatient administrative records, 27 states	1997–2014	382 State-year observations	Not reported	ICD-9-CM cannabis use disorders

prevalence of cannabis use disorders are consistent with these other national trends (see next paragraph), suggesting that the NESARC findings on increased rates of CUD are valid (Hasin and Grant, 2016).

Information on increasing time trends in rates of cannabis-related problems and CUD is available from a wide variety of large-scale data sources, many of them national in scope (Table 3). These show increasing prevalence of ICD-9-CM cannabis use disorders among patients seen in emergency rooms (Zhu and Wu, 2016), hospital inpatients (Charilaou *et al*, 2017; Shi, 2017), gastroenterology patients (Gubatan *et al*, 2016), burn treatment patients (Jehle *et al*, 2015), and in United States veterans treated in the Veterans Health Administration (Bonn-Miller *et al*, 2012). Of note, the burn treatment patients testing positive for cannabis were younger, less likely to be insured, had larger burns, and required more intensive treatment. Rates of cannabis detected among decedents of fatal motor vehicle (Brady and Li, 2014) and airplane crashes (McKay and Groff, 2016) also increased, as did rates of cannabis detected in roadside surveys of weekend nighttime drivers (Johnson *et al*, 2012).

MEDICAL AND RECREATIONAL MARIJUANA LAWS

Medical Marijuana Laws

In 1970, the Federal Drug Enforcement Agency (DEA) defined cannabis as a Schedule 1 substance, meaning no accepted medical use and high abuse potential (U.S. Department of Justice and Drug Enforcement Administration, 2017). However, since 1996, when California passed the first state medical marijuana law (MML), a total of 29 states and the District of Columbia have passed laws legalizing the use of marijuana for medical purposes (Figure 2). State MMLs share the common feature that they permit legal use of cannabis to treat medical conditions if the user has obtained medical authorization. However, the specific provisions of MMLs vary considerably (Pacula *et al*, 2015), eg, regarding the range and specificity of the permitted medical conditions, the provisions for distribution through dispensaries, permitted amounts per patient, and so on. The restrictiveness or 'medicalization (Williams *et al*, 2016, 2017)' of these laws varies as well. Table 4 shows aspects of MMLs that vary from state to state. All of these have the potential to modify the effects of MMLs, although challenges to research on the effects of these variations arise in their measures because of the between-state variability in the quality and quantity of available data.

Concerns about MMLs include their potential to increase problematic use of cannabis in the general population, hypothesized to occur through several mechanisms, including reduced perceived harmfulness and normalization of use (Pacula *et al*, 2015; Wen *et al*, 2015). Additional posited mechanisms include greater access via dispensaries and home or caregiver cultivation. Greater access increases availability, and can also normalize the idea of use and reduce perceived harm (Pacula *et al*, 2015; Wen *et al*, 2015). Table 5 shows that the percentage of Americans living in MML states has increased over time. Because early and later MMLs were passed in differing national normative contexts, their effects may vary over time (Hasin *et al*, 2017).

Before 2009, the discrepancy between the Federal and state positions meant that individuals using marijuana as specified

TABLE 4 Features of MML That May Influence Their Effects

Dispensaries
Permitted by MML (yes/no/unspecified)?
If permitted, are they operational?
Are dispensaries permitted to cultivate?
Can dispensaries be for-profit?
Can product be displayed in public view?
Is an MD required to provide full assessment and ongoing care?
Is density within areas regulated?
Are locations regulated?
Patient related
What are the permitted medical conditions (eg, pain; PTSD)?
Is patient registration recommended or required?
May patients cultivate cannabis at home?
Is there a waiting period before approval?
Is the permitted amount specified? If so, what is it?
Are minors authorized?
Caregiver related
Can caregivers cultivate? If so, how many plants are permitted?
Is caregiver registration recommended or required?
What is the number of patients permitted per caregiver?
Can caregivers charge for care?
Can caregivers possess marijuana? If so, how much?
Product related
Is testing and labeling required?
Is product packaging regulated?
Is advertising permitted? If so, is it regulated?
Are smoked products permitted?
Timing
Since the MML was passed, have its provisions been enacted?
Are there delayed effects of the MML (eg, 1, 2, 3 years)?

TABLE 5 US Population in MML States, by Year

1991	0.00
2001	0.19
2012	0.34
2016	0.63

by state MMLs were still vulnerable to federal prosecution. However, in 2009, the US Attorney General issued a memorandum instructing federal prosecutors not to prioritize prosecution of individuals compliant with state MMLs (Ogden, 2009). This gave more flexibility to MML states (Cambron *et al*, 2017), with particular impact in Colorado (Davis *et al*, 2016b; Hasin *et al*, 2017; Salomonsen-Sautel *et al*, 2014; Schuermeyer *et al*, 2014) and California (Hasin *et al*, 2017), where dispensaries proliferated. Subsequent memorandums in 2011 and 2013 further clarified these policies by indicating which areas of marijuana law enforcement were still of Federal interest (eg, limiting use among minors; Price 2014).

In states with unrestrictive MMLs (generally states with earlier-passed MMLs), the possibility that medical authorizations were obtained for recreational use is supported by the greater similarity of some medical users to recreational users than to a medically ill population (Harris *et al*, 2000; Haug *et al*, 2017; Reinarman *et al*, 2011; Walsh *et al*, 2013), and because many medical users used illicit cannabis before their medical authorization (O'Connell and Bou-Matar, 2007). However, two reports on medical marijuana users among adult NSDUH participants provide more representative information. The first (Lin *et al*, 2016), reporting only on users from MML states, indicated that among past-year cannabis users, 17% used cannabis medically. Medical and recreational users did not differ on race, education, depression, or cannabis use disorders, but medical users were more likely to report poor health and fewer substance use disorders. The second (Compton *et al*, 2017) reported on all medical cannabis users in all states, as some could use cannabis for medical purposes even if they did not live in a MML state. In this study, 9.8% of all cannabis users were medical users. Their medical use was associated with poor self-reported health, disability, older age, and older age at initiation of cannabis use. Of all medical users, 21.2% lived in states with no MMLs, suggesting that either physicians in non-MML states also recommend medical marijuana use to some patients, or some patients in non-MML states were self-medicating problems with cannabis.

Recreational Marijuana Laws

In 2012, Colorado and Washington became the first states to pass recreational marijuana laws (RMLs). Since then (Figure 2), 6 additional states passed RMLs: Alaska and Oregon (2014), and California, Nevada, Massachusetts, and Maine (2016). Consequently, 21% of the US population now lives in states where recreational use is legal. All eight of the states that passed recreational marijuana laws previously had MML.

RMLs permit legal sale and use of cannabis without the need for medical justification or authorization. Such laws may reduce discriminatory arrests of disadvantaged minorities because of biased enforcement of criminal cannabis statutes (Hall and Lynskey, 2016; Palamar *et al*, 2014), and satisfy public desire for legal cannabis use. Furthermore, RMLs have the potential to create business opportunities, jobs, and tax revenues (Forbes, 2017; McGinty *et al*, 2016, 2017a), as exemplified by Colorado (Fortune, 2016) and Washington (The Washington Times, 2016), where cannabis is now a billion-dollar-a-year business (Wang *et al*, 2017). However, RMLs are likely to increase availability, advertising, and accepting attitudes toward cannabis use, all of which may enlarge the population of cannabis users, increase the rates of adverse health or psychosocial consequences, and have unintended effects of the use of other substances (Volkow *et al*, 2014). In addition, RMLs are likely to reduce the price of cannabis (Hall and Lynskey, 2016) that may also increase its appeal. Because RMLs are recent, little is known about their impact on public health. Recognizing this, the National Institute on Drug Abuse has made studies of state marijuana laws a priority (National Institute on Drug Abuse, 2015).

RELATIONSHIP OF MARIJUANA LAWS TO TRENDS IN USE AND CONSEQUENCES

Marijuana Laws and Trends in Cannabis Potency

Among samples of illegal cannabis seized by law enforcement between 1990 and 2010 (Sevigny *et al*, 2014) analyzed by state, the mean THC potency was 9.1% in states that eventually passed MMLs and 5.6% in other states. Initial models of state effects on potency found a MML effect on subsequent cannabis potency, but this effect was no longer significant after controlling for a multitude of potential confounders. However, in states with legally operating dispensaries, the MML effect remained significant, increasing THC potency of ~ 1%.

As states increasingly pass recreational marijuana laws, the THC potency of illicit cannabis in MML states may no longer be such a salient issue. In Washington (RML passed in 2012), the average THC potency of marijuana flower for one Seattle-based retailer in 2015 was 21.2% (Washington State Marijuana Impact Report, 2016). In Colorado, where THC potency of legally marketed cannabis can range considerably, some strains have THC potencies of 28–32% (CNN, 2016). In 2016, Colorado legislators attempted to limit THC content of marketed cannabis to 16%, but this attempt failed, indicating local support for continued marketing of stronger forms of cannabis. Furthermore, although smoking remains the most common route of administration (Hall *et al*, 2016), newly popular routes of administration offer even higher THC doses (Hall *et al*, 2016). These include edibles, vaping (inhaled vapor of heated e-liquids analogous to e-cigarettes), and dabbing (inhaled vapor from heating highly concentrated forms of cannabis or hashish). The health effects of these methods are not yet known, but warrant monitoring (National Institute on Drug Abuse, 2017).

Marijuana Laws and Trends in Prenatal Exposure

No published studies were found on differences in rates of cannabis use by MML or RML state status. Unpublished results from one study (Brown *et al*, 2017) showed that in MML and non-MML states, rates of cannabis use in pregnant women did not differ significantly.

Marijuana Laws and Trends in Childhood Exposure

A study of 2005–2011 calls to poison centers for unintentional pediatric cannabis exposures showed little increase in states with no MML, an increase of 11.5% in states passing MMLs in 2005–2011, and an increase of 30.3% in states passing MMLs before 2005 (Wang *et al*, 2014). In this study, among children unintentionally exposed to cannabis, those in states with MMLs passed before 2005 were more likely to be evaluated in a health-care facility, experience major or moderate effects, and be admitted to critical care units (Wang *et al*, 2014). Another study found that calls to Colorado poison control centers for unintentional pediatric cannabis exposures between 2009 and 2015 (when medical dispensaries proliferated and recreational use was legalized) increased 34% annually, significantly greater than the 19% increase in cannabis-related calls received by poison control centers in other states (Wang *et al*, 2016a). A further breakdown of Colorado poison center calls (Wang *et al*, 2017) showed significant increases in those aged 0–8 and 9–17 years after liberalization of medical marijuana laws in 2010, and an even further increase in these ages after enactment of legalized recreational use in 2014. Thus, liberalization of marijuana laws appears related to increases in childhood nonfatal cannabis exposures.

Marijuana Laws and Trends in Adolescent Cannabis Use

Because of the potential harms of early adolescent cannabis use, concerns were raised that MMLs could increase adolescent use by conveying a message about acceptability or lack of negative health consequences, even if MML implementation was delayed or narrowly defined (Hasin *et al*, 2015b). A study using cross-sectional national data showed that adolescent cannabis use was more prevalent in MML states (Wall *et al*, 2011). However, cross-sectional associations do not necessarily indicate a causal relationship, as states with MMLs could have had higher rates of use before MML passage (ie, reverse causation). Although randomized assignment of MMLs to states would provide clarity about the direction of effect, such assignment is clearly not possible. Therefore, studies used difference-in-difference (DiD) tests to examine differences in rates in states before and after MML passage compared with contemporaneous differences during the same years in non-MML states (Angrist and Krueger, 1999; Angrist and Pischke, 2009; Hunt and Miles, 2015; Imbens and Wooldridge, 2009). These studies also controlled for many state- and individual-level confounders to sharpen conclusions on causality. Studies used MTF data from 1991 to 2014 (Hasin *et al*, 2015b), NSDUH data from 2002 to 2012 (Wen *et al*, 2015), and several other large databases (Sarvet *et al*, under review-a). Of the 17 large surveys using DiD methods spanning different states, periods, and specifications, 16 indicated no MML effects on adolescent use (Anderson *et al*, 2015; Choi, 2014; Hasin *et al*, 2015b; Keyes *et al*, 2016; Martins *et al*, 2016; Pacula *et al*, 2015; Sarvet *et al*, under review-a; Smart, 2015; Wen *et al*, 2015). Despite differences in methodology, the findings were very consistent: post-MML adolescent cannabis use did not increase compared with pre-MML levels and to national trends in non-MML states during the corresponding years. In MTF data, perceived harmfulness of marijuana use decreased and marijuana use increased following legalization of recreational marijuana use in Washington State in 2012 whereas, in contrast Colorado did not exhibit any differential change in perceived harmfulness or past-month adolescent marijuana use following legalization (Cerda *et al*, 2017).

Marijuana Laws and Trends in Adult Cannabis Use and Cannabis Use Disorders

Fewer studies are available on the relationship of MMLs to adult cannabis outcomes. A cross-sectional study using national 2004–2005 data showed an association between living in a MML state with adult cannabis use and cannabis disorders (Cerda *et al*, 2012). However, this design also did not address causality. DiD tests were therefore used to examine adult outcomes. A 15–20% post-MML increase occurred in marijuana possession arrests in major cities (Chu, 2014), and a 20% post-MML increase occurred in first-time adult marijuana admissions (Chu, 2014). Using NSDUH 2004–2013 data (Table 2) at a point when 10 states had passed MMLs, DiD tests indicated significant post-MML increases for cannabis use, daily or near-daily use, and (with 1- and 2-year time lags) CUD (Wen *et al*, 2015), an effect that remained for cannabis use among adults aged ⩾26 years in a reanalysis (Martins *et al*, 2016). Using DiD tests and three NIAAA surveys from 1991–1992 to 2012–2013 (Table 2) to compare 15 MML states with other states, post-MML effects were found on adult cannabis use and CUD (Hasin *et al*, 2017). Between 1991–1992 and 2001–2002, rates of adult use and CUD generally decreased, but in contrast, rates of adult use and CUD increased in early-MML states. Between 2001–2002 and 2012–2013, rates generally increased, with greater increases in late-MML than non-MML states. During this later time, California and Colorado showed marked increases, consistent with the proliferation of dispensaries in these two states after the 2009 Department of Justice Memo. Thus, although the research base is not extensive, existing studies are consistent in showing post-MML increases in adult cannabis-related outcomes.

Recreational Marijuana Laws

Aside from Cerda *et al* (2017) and Wang *et al* (2017) who suggest that RMLs may have further effects on child exposures or adolescent use in states that already have MMLs, little is known about the effects of recreational marijuana laws on cannabis use, or cannabis-related consequences. To our knowledge, no studies have yet been published on the relationship of RML to adult outcomes, an area that is clearly in need of studies as data become available.

EPIDEMIOLOGIC EVIDENCE ON MMLS AND CANNABIS USED AS A SUBSTITUTE FOR OPIOIDS OR ALCOHOL

Cannabis to Treat Pain and as a Substitute for Opioids

Chronic pain is common in U.S. adults (Hardt *et al*, 2008; Institute of Medicine, 2011; Nahin, 2015; Tsang *et al*, 2008). Opioids are important to treat *acute* pain, but are also widely prescribed for *chronic* pain (Levy *et al*, 2015; Volkow and McLellan, 2016) with inconsistent clinical benefits (Chou *et al*, 2014) and serious risks (Chou *et al*, 2014; Volkow and McLellan, 2016), eg, physical dependence, addiction, transition to heroin, and overdose (Okie, 2010; Paulozzi *et al*, 2012; Rudd *et al*, 2016). Therefore, despite problems associated with medical marijuana (cognitive/motor impairments (Volkow *et al*, 2016), side effects (Whiting *et al*, 2015), no standard product formulations (Thomas and Pollard, 2016)), its advantages (analgesia (Whiting *et al*, 2015), lack of fatal overdose (Hall, 2017), or transition to heroin) have led to professional calls to substitute medical marijuana for opioids (Choo *et al*, 2016), although this debate continues (Saxon and Browne, 2014). Many medical marijuana patients use it for pain relief, some as a partial or complete substitute for opioids (Boehnke *et al*, 2016; Davis *et al*, 2016a; Lucas and Walsh, 2017; Lucas *et al*, 2016; Nunberg *et al*, 2011; Piper *et al*, 2017; Reinarman *et al*, 2011), and others continuing to use or abuse prescription opioids. In an online convenience sample, participants in both MML and non-MML states used cannabis for pain (Corroon *et al*, 2017). Thus, studies of adult substitution/complementarity of cannabis and opioids are needed, including whether this occurs more in MML and RML states.

Several ecological studies of MML and rates of opioid outcomes have been conducted, based on the premise that if MMLs provide marijuana to those who need it, opioid use/misuse will be reduced. The studies found that MMLs led to lower rates of opioid prescriptions in Medicaid (Bradford and Bradford, 2017) and Medicare Part D (Bradford and Bradford, 2016a). MMLs also led to lower rates of opioid overdoses (Bachhuber *et al*, 2014; Pardo, 2016), although according to Bachhuber *et al* (2014) significance was lost after controlling for state-specific linear time trends that adjusted for differential factors changing linearly over the study period (eg, hard-to-measure attitudes or cultural changes). MMLs were also associated with decreased hospitalization for OUD (Powell *et al*, 2015; Shi, 2017) and opioids detected in fatally injured drivers (Kim *et al*, 2016) (but of all ages studied, only in those aged 21–40 years). In the single individual-level study (NSDUH 2004–2012), MML was *un*related to non-medical opioid or heroin use (Wen *et al*, 2015). Studies are thus largely but not fully consistent. The field concurs that more individual-level studies of MML and opioids are needed, controlling for important individual *and* state-level covariates (Bradford and Bradford, 2016b,2017; Finney *et al*, 2015; Hall and Lynskey, 2016). Opioid outcomes should include *medical use*, ie, prescriptions; benzodiazepine co-prescriptions (shown repeatedly (Garg *et al*, 2017; Hawkins *et al*, 2013; Hwang *et al*, 2016; Sun *et al*, 2017) to be very risky for overdose, and common in some groups, eg, veterans (Hawkins *et al*, 2015)); frequent *non-medical use*; and *consequences* of medical or nonmedical use: OUD, DUI, overdose. Studies should include state-level demographic characteristics, MML provisions, and opioid policies. Studies should also determine whether MML effects remain after controlling for important individual demographic and clinical characteristics, eg, pain or pain-related medical conditions, and other substance and psychiatric disorders (Hayes and Brown, 2014).

Adults and Alcohol

Some medical marijuana clients substitute cannabis for alcohol (Lucas and Walsh, 2017; Lucas *et al*, 2016; Nunberg *et al*, 2011; Reiman, 2009; Reinarman *et al*, 2011). In studies that used data from 1990 to 2010, passage of MMLs was followed by *decreased* alcohol-related traffic fatalities (Anderson *et al*, 2013) and binge drinking (Anderson *et al*, 2013), suggesting that cannabis was substituted for alcohol in these states. However, in NSDUH adults surveyed between 2004 and 2012, passage of MMLs was followed by *increased* binge drinking (Anderson *et al*, 2013; Guttmannova *et al*, 2016; Wen *et al*, 2015). An unpublished economics report showed that passage of MML was followed by *increases* in any drinking and alcohol-related treatment admissions, but only if the MMLs permitted dispensaries (Pacula *et al*, 2013). A state-level study using data from 1985 to 2014 showed that passage of MMLs was followed by *decreased* overall US traffic fatalities (Santaella-Tenorio *et al*, 2017), particularly in ages 25–44 years, but only in 7 states, and therefore the results were interpreted as indicating heterogeneous effects. Thus, findings on MMLs, alcohol, and cannabis have been inconsistent (Guttmannova *et al*, 2016), perhaps because of analyses of different outcomes and state-level control variables in the different studies (Guttmannova *et al*, 2016), leading to the need for further exploration in designs that could clarify the sources of inconsistent results.

Speculation about RML effects largely assume that substituting cannabis for alcohol will be better for public health (Anderson and Rees, 2014; Carnevale *et al*, 2017). Some experts have assumed that RMLs will lead to substitution of cannabis for alcohol (Anderson and Rees, 2014; Kilmer, 2017), whereas others have been less sure (Edwards, 1974; Hall and Lynskey, 2016; Hawken *et al*, 2013; Pacula and Sevigny, 2014). Whether cannabis will actually be substituted for alcohol after passage of RMLs, and whether the effects of any such substitution on public health will be positive, negative, or neutral is currently unknown.

EPIDEMIOLOGIC EVIDENCE ON MARIJUANA LAWS AND CANNABIS USED AS A SUBSTITUTE FOR PSYCHIATRIC MEDICATION

Personal and anecdotal testimonies suggest that cannabis (medical or otherwise) is effective in treating symptoms of depression and anxiety (Broadly, 2016; Grass City, 2010). Consistent with this, surveys of medical marijuana patients show that many of them use marijuana to treat these symptoms (Bohnert *et al*, 2014; Bonn-Miller *et al*, 2014; Harris *et al*, 2000; Nunberg *et al*, 2011; Piper *et al*, 2017; Reinarman *et al*, 2011; Walsh *et al*, 2017). Although theoretical reasons suggest that synthetic oral cannabinoids may be helpful for some aspects of PTSD (Haney and Evins, 2016), scientific reviews (National Academies of Sciences, 2017; Walsh *et al*, 2017; Whiting *et al*, 2015) of studies to date find no evidence for the efficacy of cannabinoids in the treatment of depression or anxiety disorders. In addition, prospective studies show adverse cannabis effects on the course of depression (Bahorik *et al*, 2017) and PTSD (Wilkinson *et al*, 2015). When medical marijuana clients are asked about actual symptom relief, less than half report such relief (Bonn-Miller *et al*, 2014); other medical marijuana clients (Swift *et al*, 2005) report return of anxiety symptoms on cessation of use, suggesting the symptoms might be due to cannabis withdrawal (Walsh *et al*, 2017). Because many cannabis withdrawal criteria are depression/anxiety symptoms (American Psychiatric Association, 2013) (Table 1), regular users may seek cannabis to obtain short-term symptom relief, unaware that this could perpetuate a longer-term withdrawal problem. Nevertheless, medical marijuana is authorized for PTSD in 21 states, and in many others, permitted conditions are vague enough that use for depression or anxiety may also be authorized. In nationally representative 2004–2005 data, participants with DSM-IV depressive or anxiety disorders were more likely to self-medicate their symptoms with cannabis if they lived in MML than non-MML states (Sarvet *et al*, under review-b). However, a more recent survey of a convenience sample suggested that self-medication of depression or anxiety with cannabis is equally common in MML and non-MML states (Corroon *et al*, 2017). Without recent data from a representative sample, whether the more recent convenience survey reflects a change or a biased result due to the sampling method remains unknown.

In data on all fee-for-service Medicaid prescriptions from 2007 to 2014, antidepressant and anti-anxiety prescriptions were lower in states with MMLs than in other states (Bradford and Bradford, 2017). In 2010–2013 data on prescriptions filled by Medicare Part D enrollees, antidepressant prescriptions fell significantly in MML states once a medical marijuana law was implemented (Bradford and Bradford, 2016a). If cannabis/cannabinoid products were effective treatments for depression or anxiety disorders, substituting cannabis for FDA-approved medication would be a positive MML result (eg, by reducing medical costs (Bradford and Bradford, 2016b)). As evidence on efficacy suggests otherwise (National Academies of Sciences, 2017; Walsh *et al*, 2017; Whiting *et al*, 2015), and as marijuana use may be due to confusion between cannabis withdrawal and depressive/anxiety disorders (Swift *et al*, 2005), such shifts in clinical care would be an adverse MML outcome. However, to understand the effects of MML and RML on use of antidepressants and antianxiety medication, large-scale studies using individual-level data (Bradford and Bradford, 2017) are needed that can include relevant state socio-economic and policy variables, and individual-level demographic and clinical covariates.

IMPLICATIONS AND FUTURE RESEARCH DIRECTIONS

The implications of changing laws, attitudes, and prevalence of cannabis use have implications for clinicians, policy makers, and the public. All should be aware that despite a lack of risk for fatal overdose or transition to heroin, both of which are serious risks for prescription opioids, cannabis is not a harmless substance, and use can involve impairments, addiction, and risks for serious consequences. In NESARC 2001–2002 data, 6.4% of those with current DSM-IV cannabis abuse and 18.1% of those with current DSM-IV cannabis dependence received any kind of intervention for drug use problems (Stinson *et al*, 2006) and of those with lifetime DSM-IV cannabis abuse or dependence, 9.8 and 34.7% received any type of intervention. Thus, drug treatment among those with cannabis use disorders was rare, and whether the treatment focused on cannabis use disorders is unknown. NESARC-III 2012–2013 data showed that among those with DSM-5 current and lifetime cannabis use disorders, 7.2 and 13.7% received any type of intervention specifically for cannabis problems (Hasin *et al*, 2016). Furthermore, despite the clear increases in adult cannabis use and related problems in the general population, the proportion of patients in substance abuse treatment whose primary substance was cannabis was 16% in 2003 and 17% in 2013 (Substance Abuse and Mental Health Services Administration and Center for Behavioral Health Statistics and Quality, 2015), showing no increase. Thus, cannabis use disorders remain seriously undertreated in the US general population.

Mental health clinicians, especially those treating younger patients or patients with affective or anxiety symptoms, should consider screening their patients for cannabis use patterns and cannabis use disorder criteria to determine whether a disorder is present, or explore with patients whether a cannabis use/withdrawal cycle may be perpetuating depressive or anxiety symptoms. Although patients may not initially be receptive to the idea that cannabis is causing or contributing to their symptoms or problems rather than alleviating them, continued discussion and some monitoring may help in this regard. Health policy makers, for example, commissioners of state or city mental health or substance abuse services should also be aware of the national trends toward increasing use and consequences, and encourage system-wide awareness of current information on cannabis use and its consequences across all professional levels of service providers. State legislators, when considering passage or modifications of medical or recreational marijuana laws, should consider increases in the occurrence of potential adverse consequences of increasingly widespread use, and design state policies for distributing, advertising, and taxing cannabis with these risks in mind. Finally, the public should be made aware of the risks as well. Public education campaigns based on exaggerated scare tactics are unlikely to be successful. However, public education efforts can be effective in such areas as reduced rates of drunk-driving fatal accidents (Niederdeppe *et al*, 2017a). Well-designed, evidence-based programs may change public attitudes in a positive, more health-promoting direction on many health policy issues involving substance use (Bachhuber *et al*, 2015; Niederdeppe *et al*, 2017b).

This review has identified a number of areas needing further research. The following are open areas of research that could be investigated using epidemiologic designs.

(a) Studies on the relationship of medical and recreational marijuana laws to indicators of driving under the influence of cannabis, or of other substances.
(b) Studies of postnatal outcomes among women using marijuana but not other substances while pregnant that may be more possible now than in previous years if women who would not consider drinking alcohol or smoking cigarettes see marijuana as a harmless way to treat pregnancy-related symptoms (The New York Times, 2017).
(c) Long-term comparisons of cognitive functioning in cannabis users and nonusers, with observation begun in childhood, before cannabis exposure.
(d) Studies of the relationship between cannabis withdrawal symptoms, diagnoses of depressive and anxiety disorders, self-medication with cannabis, and utilization of psychiatric medication.
(e) Studies examining the effectiveness of various interventions aimed at increasing public awareness of cannabis risks and their likelihood.
(f) Continued monitoring of time trends in cannabis use and consequences, overall and by demographic characteristics.
(g) Continued studies of the relationship of MML to cannabis use and consequences, and to the use of and consequences of other substances, including opioids.
(h) Studies of the relationship of RML to cannabis use and consequences, and to the use of and consequences of other substances, including opioids.

In the past 10 years, much has been learned about cannabis, its use, and its consequences. However, in this time of rapidly changing marijuana laws and attitudes, much remains to be learned in order to advance public health and to guide personal and societal decisions regarding the use of cannabis.

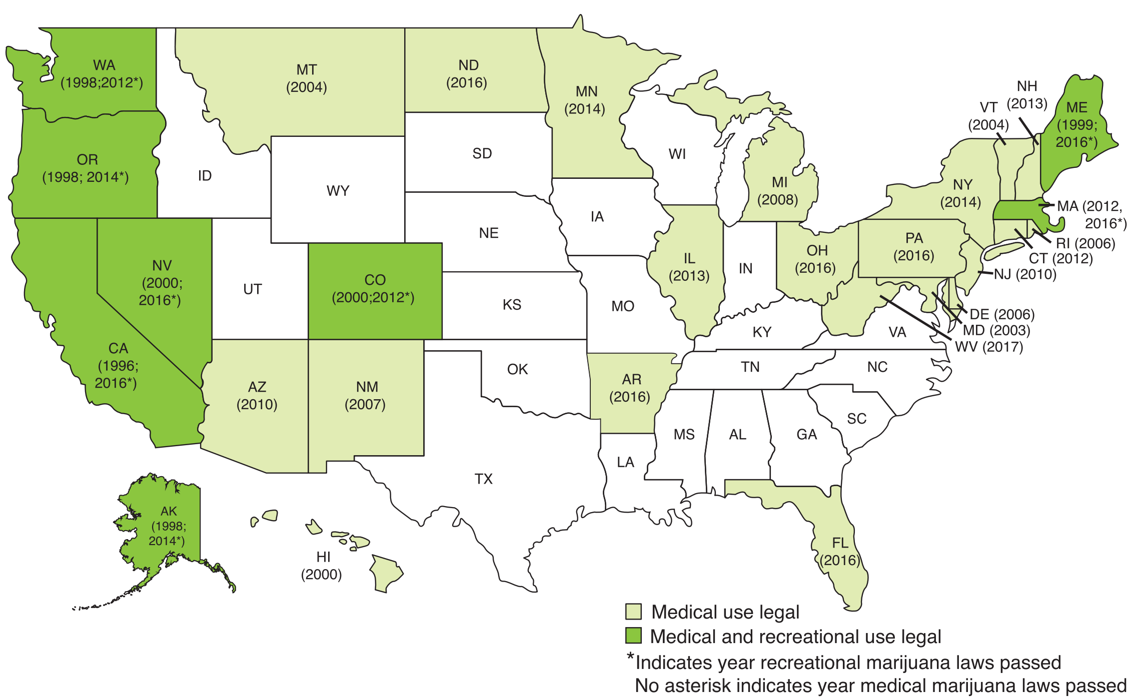

Figure 2. US states, medical and recreational marijuana laws.

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